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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY DOCKET NO.
08/219,200	03/29/94	LINSLEY	P 30436.11USO1

EXAMINER

18M1/0513

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ART UNIT	PAPER NUMBER
1806	44

DATE MAILED: 05/13/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 1/28/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 79-91 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 79-91 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). 43, 41 (same IDS)
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1806.

2. Applicant's amendments; filed 1/218/97 (Paper No. 42) , is acknowledged.
Claims 1, 3, 5-8, 18-19, 40-42, 67-76 and 78 were canceled.
Claims 79-96 were added.

Claims 2, 4, 9-17, 20-39, 43-66 and 77 have been canceled previously.
Claims 79-96 are pending.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.
This Action will be in response to applicant's arguments, filed 1/28/97 (Paper No. 42).
The rejections of record can be found in the previous Office Action (Paper No. 39).

4. Applicant should amend the first line of the specification to update the status of priority documents.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

6. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 9.
Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views). Photographs are not acceptable until a petition is granted.

7. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

The use of the trademarks have been noted in this application (e.g. SEPHADEX). They should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 88-96 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: "a method of inhibiting CD28 positive T cell activation ... thereby inhibiting T cell activation".

Applicant's amendment, filed 1/218/97 (Paper No. 42) , directs support for these claims to originally filed claims 19 and 26-28. However, the original claims recite "regulating T cell responses ... wherein said T cell responses are inhibited". The original disclosure included the original claims cited by applicant do not support inhibiting T cell activation. T cell activation encompasses a myriad of objective and subjective criteria and applicant has not provided support either for the written description or direction to inhibiting CD28 positive T cell activation in the application as-filed. While the instant disclosure supports inhibiting binding and proliferation by T cells, it does not provide support inhibiting T cell activation and what is encompassed by such a recitation. The specification does not provide blazemarks nor direction for the instant methods as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed.

Applicant is required to cancel the new matter.

10. Upon reconsideration of the instant disclosure and the art, the instant claims drawn to inhibiting T cell responses with soluble B7 and CD28 fusion proteins are considered not enabled.

The specification is objected to and claims 79-96 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as adhesion-based biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations of inhibiting cognate T:B interaction s with anti-CD28 antibodies and anti-B7 antibodies provides the basis for employing CD28Ig and B7Ig fusion proteins (see page 72, paragraph 1 of the instant specification). It is noted that B7Ig inhibited CD28-mediated adhesion in vitro to a lesser degree than the CD28-specific antibody 9.3 and that CD28Ig did not inhibit said in vitro adhesion (see page 64 of the instant specification). In addition, B7Ig in solution showed a modest enhancement of proliferation of T cells in vitro event though anti-CD28 antibody 9.3 was effective (page 65 of the instant specification). There is no evidence that CD28Ig was tested in this in vitro system or other experimental in vitro or in vivo systems that would be predictive of the therapeutic methods encompassed by the claims. There is insufficient objective evidence that accurately reflects the relative efficacy of the claimed therapeutic strategies to inhibit T cell proliferation or to prevent binding of CD28 receptor to B7 antigen, commensurate in scope with the therapeutic methods encompassed by the claimed methods.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Kahan clearly states that no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Cur. Opin. Immunol., 1992; see entire document, particularly page 558, column 2).

Blazar et al. (J. Immunol., 1996) discloses that issues such as tissue distribution, half-life, affinity and avidity obtained with these various CD28-B7-specific reagents might prove to be highly important in achieving GVHD protection. However, any conclusion regarding the efficacy of CD28/B7 blockade on altering in vivo immune response should be interpreted in light of the type of reagent infused (Blazar see page 3257, column 2, paragraph 10.

Blazar et al. (J. Immunol., 1996) discloses that anti-CD80 or anti-CD86 antibodies were ineffective in preventing T cell CD8-mediated GVHD lethality; that each antibodies was partially effective in CD4-mediated GVHD lethality and that the combination of anti-CD80 and anti-CD86 antibodies wre effective in preventing GVHD lethality in murine experimental models (see entire document, including the Abstract)

Similarly, Perrin et al. (J. Neuroimmunol, 1996) discloses that in contrast to the effective treatment of disease with CTLA-4 Ig; anti-CD80 (B7-1) attenuated the first clinical disease episode but not the relapse, anti-CD86 (B7-2) had no significant effect on the course of disease, and the combined treatment with anti-CD80 plus anti-CD86 resulted in the exacerbation of disease (see entire document). It is also noted that CTLA-4 Ig had a marked but incomplete therapeutic effect in the EAE model.

In addition, Yi-qun et al. (Intl. Immunol., 1996) discloses that their findings have a number of important implications for therapeutic approaches (see entire document, particularly Discussion, last paragraph). It is clear that inhibition of T cell response to soluble antigens will require the blocking of both B7-2 and B7-1 to be effective. More, important it is unlikely that ongoing T cell response will be susceptible to inhibition by anti-B7 reagents, for example in autoimmune diseases.

Therefore, it appears that the administration of CTLA-4 Ig can result in immunosuppression as observed in several model systems, however even in these systems the timing of CTLA-4 Ig administration relative to the antigenic exposure of the mechanism by which the foreign antigens were introduced into the host (e.g. timing, dose and site) had significant impact on the success of the intervention.

In contrast to the role that the CD28-B7 inhibitor CTLA-4 Ig appears to have in vivo, there is insufficient objective evidence in the instant application that either B7Ig or CD28Ig fusion protein alone can inhibit T cell function or interactions in vivo and the evidence above would indicate that neither would be predicted to inhibit in vivo function or interactions.

Immunosuppression and inhibition of leukocyte interactions and functions are much easier to achieve under controlled in vitro conditions that experienced in the human immunoregulatory diseases targeted by the claimed invention. Further, in animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Therefore, it should be noted that although the animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. Immunosuppression is much easier to achieve under such controlled conditions to defined antigens in mice than that experienced in the human immunoregulatory diseases targeted by the claimed invention.

The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by B7 Ig or CD28 Ig fusion proteins. The specification does not teach how to extrapolate data obtained from the disclosed in vitro assays based upon B7 Ig or CD28 Ig or from other CD28-B7 inhibitors such as antibodies or CTLA-4 Ig to the development of effective in vivo human therapeutic methods, commensurate in scope with the claimed invention. Furthermore, the disclosed uses encompassed by the claimed methods are the inhibition of transplant rejection, GVHD, autoimmunity, infectious disease and neoplasia

(see Uses In Vitro and In Vivo on pages 23-29). Based upon the evidence disclosed in the instant specification and in the art , the skilled artisan could predict the efficacy of B7 Ig or CD28 Ig fusion proteins to inhibit T cell function or interactions in the diseases encompassed by the claimed methods.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting T cell function and interactions.

Applicant arguments, filed 1/28/97 (Paper No. 42), state that the invention is directed to the discovery that B7 will recognize CD28 and vice-versa and that this recognition produces the effects claimed and, in turn, applicant is entitled to other soluble fusion proteins. However, for the reasons set forth above including applicant's own disclosure and the art, soluble B7 and CD28 fusion proteins have not met the limitations of the instant methods. Therefore, not only have immunoglobulin fusion proteins comprising B7 and CD28 have not met the claimed limitations but neither have the various soluble proteins other than said immuonoglobulin fusion proteins. Issues such as tissue distribution, half-life, affinity and avidity obtained with various CD28-B7-specific reagents on altering in vivo immune responses should be interpreted in light of the type of reagent infused. Applicant's arguments have been fully considered but are not found convincing with respect to soluble fusion proteins.

11. It is apparent that ATCC 68627 (B7Ig) and 68628 (CD28Ig) plasmids are required to practice the claimed invention (claims 87 and 94). As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the plasmids which produces these fusion proteins. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Alternatively, if the entire amino acid or nucleic acid sequence is provided in the instant application as filed, then this requirement is obviated. Applicant is requested to clarify whether the deposit requirement for the claimed plasmids has been satisfied in the prosecution history of this application already.

12. Claims 79-96 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are indefinite in the recitation of "B7" and "containing amino acid residues from about position 1 to about position 215 of the amino acid sequence corresponding to the extracellular domain of B7 antigen " because their characteristics are ambiguous and not defined. The compounds of interest are defined by an arbitrary protein name (i.e. B7). While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein and variants thereof. Others in the field may isolate the same protein and give such an entirely different name. Also, B7 can refer to a number of distinct proteins expressed on various tissues and in various animal species. Applicant should particularly point out and distinctly claim the B7 antigen by claiming characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and what the compounds are made up of. This language is vague and indefinite since it can encompass many different proteins and it is not apparent which particular antigen is being referred to. Furthermore, the recitation of the certain amino acid sequences are ambiguous and confusing since it is unclear as to what is the base amino acid sequence being relied upon.

While the specification, while being enabling for a B7 protein as sequenced by Freedman et al. (J. Immunol., 1989 (page 6, paragraph 1 of the instant specification), does not reasonably provide enablement for any B7 protein and, in turn, for any B7 fusion protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not appear to specifically define the metes and bounds of "B7" or "B7 antigen". As such, this term cannot be considered to be limited to the specific B7 antigen disclosed in the specification. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable identification of any other B7 antigen meeting the structural or functional limitations of the instant invention and it is deemed to constitute undue experimentation to determine them. Further, it is not the intention of the instant disclosure to be drawn to any B7 antigen other than the B7 antigen as defined by the Freedman et al. (J. Immunol., 1989) . Applicant has enabled only this B7 antigen and, in turn, only those sequences and extracellular domains derived from said B7 antigen. The disclosure is not commensurate in scope with the breadth of the claims.

Applicant is required to amend the claimed limitation to include a SEQ ID NO. for the B7 antigen.